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March 28, 2005

ADVERSE DETERMINATION LETTER

BY FACSIMILE &
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John F. McGuire
Executive Vice President
Biomedical Services
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

RE: United States v American National Red Cross, Civil Action No. 93-0949 (JGP)

Dear Mr. McGuire:

Food and Drug Administration (FDA) investigators inspected the American National Red Cross (ARC), Southern California Region's (Region) manufacturing and distribution facility located at 18321 Jamboree Road, Building F, Irvine, California 92612, from July 19 through August 4, 2004, and November 29 through December 13, 2004. During those inspections, the FDA investigators observed numerous deviations from the FDA law, regulations, and the Amended Consent Decree of Permanent Injunction (Decree) entered on April 15, 2003. At the conclusion of each inspection, the investigators issued a Form FDA 483, Inspectional Observations (FDA 483), attached hereto. ARC responded to each FDA 483 by letters dated October 20, 2004, and February 24, 2005. FDA has reviewed those responses. Pursuant to Paragraph VIII of the Decree, FDA is notifying ARC of its determination that ARC has violated the law, regulations, and the Decree. The violations are:

1) Failure to follow written production and process control procedure, as required by 21 CFR 211.100(b) and Paragraphs IV, IV.A.1., and VIII of the Decree. For example:

a) The Region did not follow ARC's Blood Service Directive (BSD) 94.101T, *Recalls and Market Withdrawal,* which requires physical and electronic quarantine of suspect blood and blood components to prevent release for distribution. As a result, ten units of suspect whole blood were removed from physical quarantine, manufactured into 20 blood components, and distributed in commerce. Distribution occurred after ARC had decided that the whole blood units were to be discarded due to storage temperature deviations.

On July 21, 2004, an FDA investigator reviewed Deviation Tracking System (DTS) report 2003-006-0198070, which documents a deviation that was discovered by the Region on September 26, 2003. The

investigator observed that the final status of the deviation was documented by ARC as "Closed Final." The deviation report states that "466 units were discovered inside of transporters in excess of 8 hours after transport and were logged on the Transporter Inspection Log as placed into 1-6°C storage by line staff." After the Region discovered the error, it placed the units in physical quarantine, pending a decision regarding disposition of those units by the corporate Material Review Board (cMBR) and the regional Material Review Board (MRB). On October 1, 2003, the cMRB decided to discard units that were in transporters that exceeded 6°C; the MRB similarly decided to discard all 466 units. Although the units should have been discarded under both the cMRB's and the MRB's decisions, ten of those units were manufactured into 20 components that were distributed between October 4 and 9, 2003. The ten units had been inadvertently removed from physical quarantine because the Region failed to enter the whole blood units into ARC's National Biomedical Computer System (NBCS) and place an electronic hold on those units to prevent their distribution, as required by Blood Service Directive (BSD) 94.101T, *Recalls and Market Withdrawal.* That BSD was identified during the inspection by Regional staff as the procedure relevant to this operation. ARC's Biomedical Headquarters (BHQ) also identified the BSD as a relevant procedure that the Region failed to follow in its evaluation of the deviation as a potential system-wide problem. BHQ reported its findings in Problem Report 2004-090-0645678.

According to ARC's "Non Conforming Material Report" (NCMR) dated September 26, 2003, the affected whole blood units were placed in blood transporters and delivered to the Region's Irvine facility between 5:55 p.m. and 11:30 p.m. on September 25, 2003. Although an ARC employee at the Irvine facility logged the 466 units as "placed in a refrigerator at 1-6 C" at 2:15 a.m. on September 26, 2003, Regional Quality Assurance staff discovered that the units were still in the transporters at 8:30 a.m. Pursuant to 21 CFR 640.4 (h), these units should have all been refrigerated at 1-6°C since the time they were logged in as having been stored at this temperature at 2:15 a.m. Moreover, the NCMR states that "although the blood transporters are validated for 24 hour temperature maintenance, units are only packed for 8 hours and should be repacked or placed in alternate transporters if this time is exceeded." Blood Transporter Inspection Logs completed on September 26, 2003, between 10:12 and 10:50 a.m. show the following documented temperatures for the ten whole blood units that were manufactured into 20 components and distributed:

WBN	Temps
[redacted]	9°C
	9°C
	9°C
	12°C
	13°C
	13°C
	12°C
	12°C
	12°C
	12°C

Although DTS report 2003-006-0198070 was already documented as "Closed Final," ARC was unaware that 20 components manufactured from ten whole blood units designated for destruction had been

distributed until July 21, 2004, when the FDA investigator observed discrepancies with respect to disposition of some of the 466 whole blood units. The FDA investigator asked the regional Quality Assurance Officer (QAO) to verify final disposition of the 466 units in question. On July 29, 2004, the QAO informed the investigator that the Region discovered ten of the 466 units had been manufactured into 20 components and distributed to various consignees.

b) ARC procedure, BSD 92.103T, *Deviations*, requires ARC operations staff, upon discovery of a deviation, to "... halt distribution or otherwise gain control of the product..." including "physical and electronic quarantine." As described in item 1a of this letter, ARC failed to prevent distribution of unsuitable blood or blood components by placing the units in electronic quarantine or to otherwise gain control of these ten units.

c) BSD 92.103T, *Deviations*, requires Quality Assurance to ensure that deviations are being managed properly, including completion of log entries, investigations, and development and monitoring of corrective action plans. Quality Assurance is also responsible for review and approval of corrective action plans, results of corrective action plans, and results of effectiveness checks. During the July 19-August 4, 2004 inspection, an FDA investigator observed that the documented status of DTS Report 2003-006-0198070 was "Closed Final;" however, the report had not been documented as approved by a member of the Quality Assurance staff. During the November 29-December 13, 2004 inspection, an FDA investigator requested a copy of the signed approval page, but the QAO informed him that the Region was unable to find the report with the approval signatures. The last action documented on the report was June 6, 2004. Had this step been performed, it is likely that the distribution of unsuitable products would not have occurred or would have been detected by ARC before the FDA inspection in July 2004.

2) Failure to make and record a thorough investigation, including conclusions and follow-up, of any unexplained discrepancy or failure of a lot or unit to meet any of its specifications, as required by 21 CFR 606.100(c) and Paragraphs IV, IV.A.1., IV.B., and VIII. For example:

a) The Region closed DTS report 2003-006-0198070, but its investigation and follow-up failed to prevent distribution of 20 blood components that were manufactured from ten whole blood units that ARC intended to and should have discarded due to storage temperature deviations and to detect that those components had been distributed.

The deviation documented in DTS report 2003-006-0198070 both occurred and was discovered on September 26, 2003. The last action completed is documented on the deviation report as June 6, 2004. The 20 components were distributed between October 4 and 9, 2003. On July 21, 2004, the Regional QAO informed the FDA investigator that none of the 466 units had been distributed; however, subsequent to the FDA investigator's request for verification of the disposition of the units, the Region discovered that on September 26, 2003, ten of the 466 units had been removed from physical quarantine, manufactured into 20 components, and distributed to consignees.

As stated in item 1 above, the blood components were manufactured from whole blood units that, according to cMRB and regional MRB decisions, should have been discarded, not distributed to consignees.

b) The Region's investigation of the deviation documented in DTS report 2003-006-0198070 failed to identify the responsible individual and the reason for instructions given to Regional staff to not list the 466 units in NBCS and place them on electronic hold to prevent their distribution, contrary to BSD 94.101T, *Recalls and Market Withdrawals.*

During the November 29-December 13, 2004 inspection, an FDA investigator reviewed the Region's handling of the deviation discovered during the previous inspection, including Biological Product Deviation Report (BPDR) 2004-006-0512724. That report states that "it is unclear at this time who gave the instructions, however, in an effort to avoid erroneous release of product, staff was directed to place the products in physical quarantine and to not create them in the computer." BPDR 2004-006-0512724 was approved by the Region's management and Quality Assurance on August 27, 2004; however, the Region's investigation stopped short of determining the root cause for why an individual was able to give instructions that circumvented procedures established to prevent distribution of suspect blood products.

c) The deviation description documented on DTS report 2003-006-0198070 states that "466 units were discovered inside of transporters in excess of 8 hours after transport and were logged on the Transporter Inspection Log as placed into 1-6C storage by line staff." ARC's February 24, 2005 letter states that "transporters, containing units collected on September 25, 2003, were not unpacked and were found the next morning; however, the documentation on the Blood Transporter Inspection Log, showed the units as having been placed into 1-6°C storage." Although the logs inaccurately state that the units were placed into 1-6°C storage, neither DTS report 2003-006-0198070, nor the February 24, 2005 letter, indicate that ARC investigated whether documentation on the log represents a violation of the requirement under 21 CFR 606.160(a)(1) to "maintain records concurrently with the performance of each significant step in the collection, processing ... of each unit of blood and blood components so that all steps can be clearly traced," and if so, to develop a corrective and preventive action plan for that aspect of the deviation.

d) ARC did not thoroughly conduct and document its follow-up to BPDR 2004-006-0512724, which was opened on July 28, 2004, after FDA discovered distribution of blood components that were to be discarded. ARC's follow-up is described in its October 20, 2004 letter to FDA and in the preventive action section of the BPDR. Specifically,

i) DTS report 2003-006-0198070 states that "the Associate Director of Manufacturing Operations will develop a local procedure to instruct lab staff how to re-ice blood transporters." During the November 29-December 13, 2004 inspection, an FDA investigator discovered that no local operating procedure had been developed and that manufacturing staff do not perform icing or re-icing of blood in held transporters. ARC's February 24, 2005 letter states that "the preventive action documented in the problem report (2003-006-0198070) does not accurately reflect the events that occurred." The letter explains that a different preventive action was developed, but not documented on the DTS report, and that a new deviation report was opened on December 22, 2004, to address the later error.

ii) A July 9, 2004 ARC meeting with Quality Assurance staff regarding confirmation that products are disposed of in accordance with MRB decisions is documented as having occurred on July 6, 2004, and contains no specific reference to that topic. The meeting notes include under an MRB

heading the statement, "We need to keep closer tabs." There is no information under the heading to indicate whether the discussion involved blood product disposition.

iii) A July 14, 2004 meeting was described as part of ARC's follow-up to BPDR 2004-006-0512724 in the October 20, 2004 letter and the preventive action section of the BPDR. During this meeting, ARC discussed confirmation of blood product disposition in accordance with MRB decisions. Although this meeting is described by ARC as a significant part of the follow-up, it was not documented. During the November 29-December 13, 2004 inspection, the QAO informed an FDA investigator that no record of the meeting exists.

3) Failure to maintain written standard operating procedures that include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components for transfusion and further manufacture, as required by 21 CFR 606.100(a) and Paragraphs IV, IV.A.1., IV.B.17.b., and VIII. For example:

During the July 19-August 4, 2004 inspection, after observing units of blood that were segregated and labeled as quarantined, an FDA investigator noted that 66 potentially unsuitable blood products had not been placed on electronic hold. During interviews, the investigator learned of apparent confusion among Regional staff about responsibility for placing electronic holds on blood products that are potentially unsuitable. Although BSD 48.201M, *Component Retrieval Based on Other Non-Conforming Information,* requires the person who initiates an investigation to ensure the appropriate information, such as a hold, is applied electronically to donations and products, a Regional supervisor told the FDA investigator that "it was a grey area as to who initiates the electronic holds." This observation was item 1b on the FDA 483 issued at the conclusion of the July 19-August 4, 2004 inspection.

During the November 29-December 13, 2004 inspection, the FDA investigator reviewed Problem Report 2004-006-0527907, which was opened in response to FDA 483 item 1b. The Problem Report describes a corrective action that requires additional steps for communication and verification to ensure that potentially unsuitable units are electronically controlled. The FDA investigator observed that the additional steps in the process were not established in writing. The firm's October 20, 2004 letter to FDA also describes the additional steps but does not address establishing them in written procedures to be available to and followed by ARC employees.

This list is not intended to be an all-inclusive list of deficiencies at your establishment. FDA has reviewed ARC's October 20, 2004 and February 24, 2005 responses to the FDA 483s that were issued on August 4, 2004 and December 13, 2004, respectively. FDA will verify the promised corrective actions and evaluate their effectiveness during future inspections of ARC facilities.

* * *

In addition to the violations cited above, FDA has the following comment:

During the November 29-December 13, 2004 inspection, the investigator reviewed the Region's notification of consignees who received the 20 blood components that had been distributed despite the cMRB decision to discard the 466 units associated with DTS Report 2003-006-0198070. Paragraph X.E. requires ARC to notify consignees when unsuitable blood or blood components have been

distributed. In FDA's view, this notice was not accurate because the investigator noted that the "Urgent: Biological Recall" notices sent to consignees contained the following inaccurate statement regarding the reason for a recall, "The temperatures of the shipments were within the acceptable range despite the shipping containers being beyond the validated 24-hour period."

* * *

Paragraph VIII of the Decree provides that "[i]n the event that FDA determines, based upon inspection... review of ARC records, or other information that comes to FDA's attention ... that ARC is not following any SOP that may affect donor safety or purity or labeling of blood or any blood component ... has violated the law; has failed to fully comply with any time frame, term or provision of this Order ... then FDA may order ARC to come into compliance with the law, ARC SOPs, or this Order, assess penalties, and/or take any step that FDA deems necessary to bring ARC into compliance with the law, ARC SOPs, and this Order."

For the reasons stated above, FDA has determined that ARC did not comply with the law, ARC SOPs, and the Decree. FDA has repeatedly notified ARC regarding its quality assurance deficiencies and failures to follow its own SOPs, including its failure to properly quarantine suspect product to assure that unsuitable products are not distributed. Indeed, the Decree specifically addresses this issue. See Paragraph IV.B.17. Therefore, FDA orders ARC to do the following:

1) Within 120 days of receipt of this letter, perform a system-wide review of failures to apply electronic holds that have occurred since July 8, 2003, through the date of this letter, and report in writing to FDA the results of that review, including the number of unsuitable blood products distributed as a result of those failures and the Regions in which those failures have occurred.

2) Within 30 days of receipt of this letter, report the status of System Problem 702 in writing to FDA. System Problem 702, which described continuing problems with controlling unsuitable products, was reported to FDA on July 8, 2003, in accordance with Paragraph IV.B.2. of the Decree. [See Bates pages 030083-030101.]

3) Within 30 days of receipt of this letter, perform a retroactive review beginning one year prior to the date of this letter to ensure that the Southern California Region has complied with cMRB and MRB decisions to discard blood and blood components and report the results to FDA.

4) Within 30 days of receipt of this letter, report to FDA the status of the change to use E120 white boxes to transport blood from collection sites to the Region's Irvine facility, as described in Change Control Plan 04-174, a copy of which was provided to the investigator during the November 29-December 13, 2004 inspection. The report must include implementation dates, identify related SOPs, describe training provided to affected staff, and document effectiveness of the modification to resolve the problems described on page 2 of the Plan.

5) In the firm's response to the July 19-August 4, 2004 inspection, ARC described as its preventive action a detailed new instruction to communicate electronic holds and verify receipt of facsimile transmissions to ensure that potentially unsuitable units are electronically controlled. Within 30 days of

receipt of this letter, provide FDA with a copy of the written procedure that includes those instructions and state the implementation date. Also, report to FDA whether ARC has reviewed all procedures that contain steps to control potentially unsuitable units to identify any omissions in identification of personnel responsible for completing specific steps and any gaps in communication.

6) During the November 29-December 13, 2004 inspection, an FDA investigator observed two Blood Transporter Inspection Logs with differing entry times for the 466 units of whole blood that were the subject of DTS report 2003-006-0198070. The FDA 483 states that ARC has no written procedure for completing two such records. ARC's February 24, 2005 response letter states that, as part of its investigation of DTS report 2003-006-0198070, the QAO asked the staff to verify transporter conditions and record the results on a second Blood Transporter Inspection Log in order to provide the MRB with supplemental information. Both records were retained. Within 30 working days of receipt of this letter, report to FDA in writing how ARC intends to ensure that process control records used to document investigative activities will be readily and reliably distinguishable from actual process control records.

Pursuant to Paragraph IX of the Decree, FDA intends to fine ARC $2,000 for each of 270 days from July 19, 2004, the date FDA issued the 482 initiating the inspection in which it discovered the problem involving the unsuitable units, back to October 23, 2003, for a total of $540,000.

As provided in the Decree, if ARC agrees with this adverse determination, it shall within 20 days of receipt of this letter, notify FDA of its intent to come into compliance with the Decree and submit a plan to do so. If ARC disagrees with FDA's adverse determination, it shall respond in writing within 20 days of receipt of this letter, explaining its reason for disagreeing with FDA's determination. Your response must be submitted to me at the Food and Drug Administration, Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215, with a copy to Jesse Goodman, M.D., M.P.H., Director, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852.

Sincerely yours,

Lee Bowers
Director, Baltimore District

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